Combination Chemotherapy of Adult Acute Lymphoblastic Leukemia With Randomized Central Nervous System Prophylaxis

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Although major progress has been made in the treatment of childhood leukemia, the optimal chemotherapy of adult lymphoblastic leukemia (ALL) in adults has been unclear. In addition, the value of central nervous system prophylaxis (CNS-P) in adults has been assumed, but not established in a systematic fashion. The Southeastern Cancer Study Group has completed a prospective study in which the use of vincristine plus low-dose methotrexate and high-dose prednisone in adult acute lymphoblastic leukemia has produced an 80% (79/99) complete remission rate in patients age 15 yr and over. Younger patients had a significantly higher remission rate but no increase in remission duration. This induction regimen was associated with minimal toxicity. Random assignment to CNS-P or to no prophylaxis, after a multidrug consolidation regimen, has demonstrated a significant prolongation of CNS relapse-free interval (p = 0.008) in favor of CNS-P. CNS-P did not improve hematologic remission duration or survival. All complete remitters were maintained on mercaptopurine, methotrexate, and cyclophosphamide with pulses of prednisone and vincristine; the median time from remission to either hematologic or CNS relapse was 19.3 mo after CNS-P, and survival for these patients was 26.1 mo. We conclude that our current induction regimen is highly effective in adult ALL and that CNS prophylaxis is indicated in such patients.

A MINORITY of adults with acute leukemia have morphological and other features of their disease consistent with childhood lymphoblastic leukemia. However, the response rate to “induction” chemotherapy has been lower and the response duration has been considerably shorter in adults. Although prophylaxis against central nervous system (CNS) leukemia has been a major advance in the management of childhood leukemia, its value in adults has been unclear. In view of multiple complications of CNS prophylaxis that have been reported and uncertainty about the frequency of CNS leukemia in adults, the Southeastern Cancer Study Group began a controlled trial in 1972. We sought to confirm the promising results of an earlier Group study that induced remissions with vincristine plus low-dose methotrexate and high-dose prednisone. A maintenance drug schedule, based on a regimen used successfully in children, was to be preceded by a multidrug consolidation regimen. In anticipation of slow case accrual in this uncommon disease, we chose to study only one question in a prospective randomized fashion, namely, is cranial radiation plus intrathecal methotrexate of value in preventing leukemic meningitis in adults?

MATERIALS AND METHODS

Untreated patients age 15 yr and over with a diagnosis of ALL were eligible after written informed consent. The morphological diagnosis was made by the individual investigator using the following criteria: Auer rods must not be present; megaloblastic erythropoiesis and cytoplasmic granules must be minimal; leukemic cells must have no more than a moderate amount of cytoplasm; the degree of marrow infiltration and the uniformity of leukemic cells must be fairly high.

Eighty-eight of the cases evaluable for induction had slides reviewed by the senior author, who agreed with each investigator about the diagnosis; the other 11 evaluable cases did not have slides available for this review. Special histochemical stains were encouraged but not required; immunologic and other special studies were not routinely done. No attempt was made to subclassify the ALL cases morphologically.

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Supported in part by USPHS grants from the National Cancer Institute, NIH.

Submitted April 18, 1979; accepted October 3, 1979.

The following members of the Southeastern Cancer Study Group participated in and the following USPHS grants supported this study: R. Burson, M. Campbell, J. Carpenter, J. Durant, R. Gams, D. Lineberry, G. Omura, M. Poon, and J. Prechel (University of Alabama in Birmingham, CA-03013, CA 19657 and CA 24456); H. Silberman (Duke University, CA-03177); H. Cohen (Durham V.A. Hospital, CA-05634); J. Butts, C. Corley, L. Hoffner, C. Huguley, H. Kann, J. Keller, M. Robertson, W. Vogler, and E. Win lum (Emory University, CA 03227 and CA 11263); F. Faguet and C. Wright (Medical College of Georgia, CA 06807); Y. Ahn, H. Lesser and M. Troner (University of Miami, CA 05641); S. Fischer, R. Joseph, R. Smalley, and R. Wright (Temple University, CA 07961); V. Loeb (Washington University, CA 03376); N. Maldonado, F. Roberts, and E. Velez-Garcia (University of Puerto Rico, CA 12223); S. Gregory and W. Knospe (Rush Medical College, CA 12840); S. Krauss and T. Sonoda (University of Tennessee, Knoxville, CA 13237); K. Tornay (New Orleans V.A. Hospital, CA 13249); W. Forman, R. Kellerman, A. Lubin, and A. Rassiga (Case Western Reserve University, CA 15584); W. Arrow smith (Ochsner Clinic, CA 15578); C. Neely (University of Tennessee, Memphis, CA 17027); G. Broun and P. Petruska (St. Louis University, CA 17214); D. De Simone and J. Gockerman (University of Kentucky, CA 20255); O. Martelo (University of Cincinnati); W. Hanson (Radiological Physics Center, M. D. Anderson Hospital, Houston, Texas).

Presented in part to the American Society of Clinical Oncology, April 4, 1978, Washington, D.C.

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0006-4971/80/5502-00/6$01.00/0
Treatment Program Induction

The induction treatment was given in 20-day cycles, using a single daily dose of prednisone, 350 mg/sq m orally for 10 days, then 70 mg/sq m every other day through day 20. Vincristine, 1 mg/sq m intravenously once weekly, and methotrexate, 2 mg/sq m orally every 6 hr for 4 doses repeated twice weekly, were started on day 1. The entire cycle was to be repeated as long as progressive improvement continued. Allopurinol, hydration, blood products, and antibiotics were given as needed. A complete remission was diagnosed when the marrow was normocellular with 0%-5% blasts, erythroid activity at least 15%, granulocytic elements at least 25%, the blood had more than 10 g/dl hemoglobin concentration, more than 2000 granulocytes and more than 100,000 platelets, and there were no relevant physical findings. Spinal fluid examination was not required to diagnose complete remission.

Consolidation

Once a complete remission (CR) was confirmed, "consolidation" treatment was given: arabinosyl cytosine (ARA-C), 100 mg/sq m intravenously, plus 6-thioguanine, 100 mg/sq m orally, every 12 hr times 10 doses; approximately 9 days later, asparaginase, 500 IL/sq m, was given intravenously daily times 5, plus vincristine, 1 mg/sq m on days 1 and 5, and prednisone, 50 mg/sq m daily times 5, as a second consolidation.

At the end of the consolidation phase, a repeat bone marrow examination was done to confirm continuing marrow remission. In addition, a lumbar puncture was done with cytocentrifugation of the spinal fluid. If the lumbar puncture showed 10 or more mononuclear cells or any definite blast cells, cranial radiation and intrathecal spinal fluid. If the lumbar puncture was repeated; if normal, no further treatment was required to diagnose complete remission.

CNS Prophylaxis

If the spinal fluid was normal and the bone marrow normal, patients were randomly assigned to 3 wk of systemic mercaptopurine, 50 mg/sq m/day, plus cyclophosphamide, 200 mg/sq m weekly, or without intrathecal methotrexate and cranial radiation, 2400 rad in 12 fractions over 2.5 wk through opposing lateral ports to the head, with each field being treated each day. A shaped port was used to include the extensions of the meninges. The treatment portals were to include the whole brain, excluding the occipital lobes, which were to be adequately shielded. The anterior superior and posterior boundaries of the field were to extend at least to the external table of the bones of the calvarium and to the posterior wall of the orbit. Inferiorly, the line was to extend to the auditory canal, including the entire middle fossa (temporal lobes), and from here to follow the clivus, extending posteriorly to the level of C-2. Shielding materials were to have at least five half-value layers for megavoltage energies. Localization films on the treatment machine were to have at least five half-value layers for megavoltage energies. Localization films on the treatment machine were to be obtained on every patient. A supravoltage source was required with the treatment distance being at least 70 cm to the skin or to the isocenter. Preservative-free intrathecal methotrexate, 10 mg/sq m (no maximum dose), was given twice weekly for 5 doses using Elliott’s B solution as diluent.

Maintenance

Nonrandomized maintenance therapy for 24 mo included 6-mercaptopurine, 50 mg/sq m orally daily, cyclophosphamide, 200 mg/sq m orally or intravenously weekly, and methotrexate, 20 mg/sq m orally, intramuscularly, or intravenously weekly. "Inducer dosing" with vincristine, 1.5 mg/sq m intravenously weekly times 3, plus prednisone 50 mg/sq m daily times 14, was repeated every 8 wk, after a follow-up bone marrow examination to confirm the remission.

At the end of 24 mo maintenance, bone marrow examination and lumbar puncture were repeated; if normal, no further treatment was given as long as remission persisted, but monthly blood counts and every 2 mo bone marrows were to be done thereafter. No additional spinal taps were done except on clinical indication. Documentation of a bone marrow relapse marked the end of the remission. If CNS relapse occurred while still in hematologic remission, CNS therapy was given as described above and the patient remained on study. All patients were followed for the duration of remission and survival.

Dose Adjustment

Induction. Vincristine could be discontinued for disabling paresthesias or weakness.

Consolidation. Asparaginase could be discontinued for anaphylaxis, abdominal pain, or an increased serum amylase.

CNS phase. If the granulocyte count was less than 2000 or platelet count less than 100,000/μl, the 6-MP and cyclophosphamide were omitted; if the granulocyte count was less than 1500 or the platelet count less than 75,000/μl, the intrathecal methotrexate was delayed until blood counts improved.

Maintenance phase. The doses of 6-MP, cyclophosphamide, and methotrexate were to be titrated up or down proportionately to maintain the white count at 3000–4000. Cyclophosphamide was to be discontinued if hemorrhagic cystitis occurred. Hematologic toxicity was graded according to SEI criteria. A granulocyte toxicity score of 1 + equals fall from normal to 0.75-1.5 × 10⁹/liter or from 1.5-3.0 × 10⁹/liter to 0.20-0.75 × 10⁹/liter; 2 + indicates a fall from normal to the range of 0.20-0.75 × 10⁹/liter or from the range of 1.5-3.0 × 10⁹/liter to <0.20 × 10⁹/liter. A platelet toxicity score of 1 + equals fall from more than 130 × 10⁹/liter to 50-100 × 10⁹/liter or from 100-130 × 10⁹/liter to 10-50 × 10⁹/liter; 2 + indicates a fall from <130 × 10⁹/liter to the range of 10-50 × 10⁹/liter or from the range of 100-130 × 10⁹/liter to <10 × 10⁹/liter. A score of 3 + toxicity indicates life-threatening infection or bleeding associated with blood count depression.

Statistical Methods

Survival and remission curves were plotted according to the technique of Kaplan and Meier. The curves were statistically compared by the generalized Wilcoxon technique of Gehan.
RESULTS

One-hundred-fourteen (114) patients were entered from August 1972 through June 1978 and have had their review completed. Nine were not eligible (prior therapy, 3; acute myelogenous leukemia, 3; blastic phase of chronic myelogenous leukemia, 1; prior lymphoma, 2). 3 had major protocol violations during the induction phase, and 3 refused to continue therapy. Thus, 99 were evaluable for induction. Their pretreatment characteristics are shown in Table 1.

Table 2 shows the outcome of induction, consolidation, and the randomized treatment phase (chemotherapy plus or minus CNS prophylaxis). Seventy-nine patients (80%) achieved complete remission, 27 within 4 wk; 30 took 4–6 wk, and 22 required more than 6 wk of treatment. The induction regimen was generally well tolerated. However, two patients died of pneumocystis infection in complete remission after requiring multiple cycles of induction therapy. One patient developed urate nephropathy despite the use of allopurinol. Two patients developed a transient steroid psychosis, and five patients developed hyperglycemia during induction. One patient had acute pancreatitis attributed to asparaginase. One patient had transient paraplegia after intrathecal methotrexate. During the CNS phase, 18% of patients receiving prophylaxis had headaches; 30% had nausea compared with 15% of those receiving chemotherapy only. No late sequelae of the cranial radiation have been noted to date on the semiannual follow-up forms, although no specific neurologic testing is called for in the protocol. One patient developed hemorrhagic cystitis requiring cessation of cyclophosphamide. Several patients developed transient liver function abnormalities, but none had drug toxicity established as the cause. Other aspects of toxicity are shown in Tables 3 and 4.

Table 3 shows response by age for induction; in the age group 15–23, the complete remission rate was 90%; of the 5 failures, 3 achieved normal marrow and blood counts, but 2 of them had persistent splenomegaly and the other had residual adenopathy. In those aged 24 and older, the complete remission rate was 67%, which is significantly lower (p = 0.01). If one chooses age 20 as a break point, the CR rate was 92% (33/36) for those aged 15–20, and 73% (46/63) for those aged 21 and over (p = 0.03).

Of 71 patients remaining in CR at the end of consolidation, 2 were not randomized to the CNS phase because of overt CNS leukemia; after CNS therapy, one has had a CNS relapse and the other a hematologic relapse. Of 69 who were randomized, 2 refused CNS prophylaxis and were lost to follow-up. Two others who were randomized to no prophylaxis were considered ineligible because of poor compliance and major medication errors early in this phase of treatment; one subsequently had a CNS relapse and the other a hematologic relapse. Two patients had incomplete records. One other patient was taken off protocol because of what was thought to be intercurrent illness shortly after completing the CNS prophylaxis but died in hematologic relapse. Thus, there were 62 patients evaluable for the randomized phase of the study.

Eleven of 34 evaluable patients in the no-prophylaxis group have had a CNS relapse. Of 28 evaluable patients receiving cranial radiation and intrathecal methotrexate as prophylaxis, 3 had a CNS relapse. The difference between the two groups is significant at the p = 0.03 level (x² = 4.93). Since this calculation does not take into account the time at risk for CNS
relapse, the CNS relapse-free interval for both groups was plotted from the end of the CNS prophylaxis phase; this parameter is also significantly different ($p = 0.008$) in favor of CNS prophylaxis (Fig. 1). The median time has not been reached for either group, but for those who have had a CNS relapse, the median time from the end of the prophylaxis phase to this event is 13 mo for the treated group and 7 mo for the controls. The estimated CNS relapse rate is 7% versus 2% at 6 mo, 42% versus 6% at 12 mo, and 42% versus 19% at 24 mo for the no-prophylaxis group and the CNS prophylaxis group, respectively. However, hematologic remission duration (Fig. 2) and survival (Fig. 3) are not significantly different for the two groups. Not shown in these figures are the median remission duration (16.9 mo) for all complete remitters (14.7 mo for ages 15–20 versus 20.4 mo for older patients, $p = 0.671$) and the median survival (24.2 mo) for all patients evaluable for induction (21.5 mo for ages 15–20 versus 24.9 mo for age 21 plus, $p = 0.348$). Age was not a significant factor ($p = 0.31$) in relation to CNS relapse-free interval after accounting for CNS prophylaxis ($p = 0.04$).

Twenty-five patients receiving cranial radiation as part of their CNS prophylaxis had this aspect of their treatment reviewed in detail. Fourteen had the dose verified by the Radiological Physics Center, Houston, Texas, to within ±5% of protocol requirements; two had a low dose. In another eight cases, the institution had not been visited by the Radiological Physics Center staff, and in one case, the equipment had been removed. The port films were available for review in 19 of 25 cases; 7 of these were judged not acceptable in regard to treatment volume. The treatment program itself met protocol requirements in 13 cases, was acceptable with minor variations in another 9, and was
not acceptable in 3. In regard to the 3 patients who had a CNS relapse in spite of CNS prophylaxis, the port film in one showed an inadequate treatment volume; the second had a low dose (2200 rad instead of 2400) and neither the dose nor the treatment volume could be verified in the third. It should be noted that all of these patients received intrathecal methotrexate as well, so the relative importance of these protocol deviations is unclear.

Of 54 evaluable patients in the maintenance phase, 16 completed 2 yr of maintenance treatment; of these, 5 have had a marrow relapse and 11 remain in hematologic remission from 1 to 27 mo posttreatment. Thirty-eight have not completed the maintenance phase, 25 because of relapse; 13 remain in remission in the maintenance phase. Of the 16 who completed maintenance, 8 had received CNS prophylaxis with 2 marrow relapses (at 1.5 and 6 mo); of the others, 3 had a marrow relapse (at 1, 1.5, and 4 mo after completing treatment). There have been no late CNS relapses in either group.

Potential prognostic variables (age, sex, hemoglobin level, platelet count, white count, splenomegaly, hepatomegaly, mediastinal or other adenopathy) were examined in multivariate fashion, but none were predictive of remission rate or duration except age versus remission rate ($p = 0.01$, $\chi^2$ test of significance).

DISCUSSION

In any large series of adults with ALL, prednisone plus vincristine produces approximately a 50% remission rate,1 compared with over 90% in children.7 Several reports have indicated an improved remission rate in adults by the addition of anthracyclines or asparaginase. Woodruff8 has tabulated the results of such trials, showing adult remission rates of about 75% for prednisone plus vincristine plus an anthracycline in some recent studies, with median remission durations ranging from 7.5 to 25 mo. In general, teenagers have had a higher remission rate.

One of the larger trials was reported by Lister et al.19 in which 71% (36/51) of adults achieved CR using prednisone plus vincristine plus adriamycin plus asparaginase; the remission rate was 79% (15/19) in those aged 15–20 and 66% (21/32) in older patients, but there was no correlation between age and remission duration, as in the present report. The predicted median remission duration was 18.5 mo and the survival 27 mo. All patients in that trial were to receive CNS prophylaxis; 3 of 30 who received it had their initial relapse in the central nervous system.

Henderson and Glidewell14 reported a study of prednisone plus vincristine plus asparaginase in ALL patients aged 20 and older, adding daunorubicin in those not in remission by 4 wk. The CR rate was 72%, and median remission duration 15 mo. Dowling et al.15 used prednisone, vincristine, and Adriamycin for induction in 25 adults aged 15 plus; 4 were considered not evaluable; 20 achieved CR. Remission duration after a multiple drug consolidation and maintenance program appeared to be longer than with their previous protocol. All patients in those studies received CNS prophylaxis.

The present study indicates that the addition of low-dose methotrexate to vincristine plus high-dose prednisone can produce a high complete remission rate (80%), especially in those aged 15–20 (92%), with minimal toxicity. When this teenage group is excluded, the median remission duration is actually a bit longer, 20.4 mo, and the remission rate (73%) is not inferior to the general experience cited by Woodruff.1 It has been assumed that the benefits of CNS prophylaxis in children would apply to adults, but this has not been previously evaluated in a systematic manner. The present study establishes that CNS prophylaxis is of value in decreasing the occurrence of CNS relapse in adults with lymphoblastic leukemia.

Although there is currently no advantage regarding hematologic remission duration or survival, it is of interest that the effect of CNS prophylaxis on hematologic remission duration in children is not seen during the first 24 mo of remission.7 It is likely that the full impact of CNS prophylaxis on adult lymphoblastic leukemia will not become apparent until better systemic therapy is developed.

The relative importance of the consolidation program and of the specific maintenance program that we used cannot be stated. Further improvements are clearly needed, especially in regard to remission induction in older adults, reduction in the CNS relapse rate after CNS prophylaxis, and increased hematologic remission duration. Identification of other poor-risk factors, such as T-cell ALL, Burkitt-type leukemia, blastic CML presenting as ALL, extreme leukocytosis, or extensive tissue infiltration,1 may help to identify subcategories in which new approaches will be required.

ACKNOWLEDGMENT

L-Asparaginase, preservative-free methotrexate for intrathecal administration, and Elliot’s B solution were supplied by the Division of Cancer Treatment, National Cancer Institute. The human investigations described herein were performed after approval by the Human Investigations Committee of each participating institution and in accord with assurances filed with and approved by the Department of Health, Education and Welfare.
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